ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Emtricitabine/Tenofovir disoproxil Krka d.d. 200 mg/245 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300.7 mg of tenofovir disoproxil succinate or 136 mg of tenofovir).

Excipient(s) with known effect
Each film-coated tablet contains 80 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Emtricitabine/Tenofovir disoproxil Krka d.d. film-coated tablets are blue, oval, biconvex tablets, of dimensions 20 mm x 10 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Emtricitabine/Tenofovir disoproxil Krka d.d. is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults (see section 5.1).

Emtricitabine/Tenofovir disoproxil Krka d.d. is also indicated for the treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents (see section 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Emtricitabine/Tenofovir disoproxil Krka d.d. should be initiated by a physician experienced in the management of HIV infection.

Posology

Adults and adolescents aged 12 years and older, weighing at least 35 kg: One tablet, once daily.

Separate preparations of emtricitabine and tenofovir disoproxil are available for treatment of HIV-1 infection if it becomes necessary to discontinue or modify the dose of one of the components of Emtricitabine/Tenofovir disoproxil Krka d.d.. Please refer to the Summary of Product Characteristics for these medicinal products.

If a dose of Emtricitabine/Tenofovir disoproxil Krka d.d. is missed within 12 hours of the time it is usually taken, Emtricitabine/Tenofovir disoproxil Krka d.d. should be taken as soon as possible and the normal dosing schedule should be resumed. If a dose of Emtricitabine/Tenofovir disoproxil Krka d.d. is missed by more than 12 hours and it is almost time for the next dose, the missed dose should not be taken and the usual dosing schedule should be resumed.

If vomiting occurs within 1 hour of taking Emtricitabine/Tenofovir disoproxil Krka d.d., another tablet should be taken. If vomiting occurs more than 1 hour after taking Emtricitabine/Tenofovir disoproxil Krka d.d. a second dose should not be taken.

Special populations

Elderly: No dose adjustment is required (see section 5.2).

Renal impairment: Emtricitabine and tenofovir are eliminated by renal excretion and the exposure to emtricitabine and tenofovir increases in individuals with renal dysfunction (see sections 4.4 and 5.2).

Adults with renal impairment:
Emtricitabine/Tenofovir disoproxil Krka d.d. should only be used in individuals with creatinine clearance (CrCl) <80 mL/min if the potential benefits are considered to outweigh the potential risks. See Table 1.

Table 1: Dosing recommendations in adults with renal impairment

	Treatment of HIV-1 infection
Mild renal impairment (CrCl 50-80 mL/min)	Limited data from clinical studies support once daily dosing (see section 4.4).
Moderate renal impairment (CrCl 30-49 mL/min)	Administration every 48 hours is recommended based on modelling of single-dose pharmacokinetic data for emtricitabine and tenofovir disoproxil in non-HIV infected subjects with varying degrees of renal impairment (see section 4.4).
Severe renal impairment (CrCl < 30 mL/min) and haemodialysis patients	Not recommended because appropriate dose reductions cannot be achieved with the combination tablet.

Paediatrics with renal impairment:
Not recommended for use in individuals under the age of 18 years with renal impairment (see section 4.4).

Hepatic impairment: No dose adjustment is required in patients with hepatic impairment (see sections 4.4 and 5.2).

Paediatric population:
The safety and efficacy of emtricitabine/tenofovir disoproxil in children under the age of 12 years have not been established (see section 5.2).

Method of administration

Oral administration. It is preferable that Emtricitabine/Tenofovir disoproxil Krka d.d. is taken with food.

The film-coated tablet can be disintegrated in approximately 100 mL of water, orange juice or grape juice and taken immediately.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients with HIV-1 harbouring mutations

Emtricitabine/Tenofovir disoproxil Krka d.d. should be avoided in antiretroviral-experienced patients with HIV-1 harbouring the K65R mutation (see section 5.1).

Patients with hepatitis B or C virus infection

HIV-1 infected patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. Physicians should refer to current HIV treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV).

In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products. See also under *Use with ledipasvir and sofosbuvir or sofosbuvir and velpatasvir* below.

Tenofovir disoproxil is indicated for the treatment of HBV and emtricitabine has shown activity against HBV in pharmacodynamic studies but the safety and efficacy of emtricitabine/tenofovir disoproxil have not been specifically established in patients with chronic HBV infection.

Discontinuation of Emtricitabine/Tenofovir disoproxil Krka d.d. therapy in patients infected with HBV may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Emtricitabine/Tenofovir disoproxil Krka d.d. should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

Liver disease

The safety and efficacy of emtricitabine/tenofovir disoproxil have not been established in patients with significant underlying liver disorders. The pharmacokinetics of tenofovir has been studied in patients with hepatic impairment and no dose adjustment is required. The pharmacokinetics of emtricitabine has not been studied in patients with hepatic impairment. Based on minimal hepatic metabolism and the renal route of elimination for emtricitabine, it is unlikely that a dose adjustment would be required for Emtricitabine/Tenofovir disoproxil Krka d.d. in patients with hepatic impairment (see sections 4.2 and 5.2).

HIV-1infected patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal and bone effects in adults

Renal effects
Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil (see section 4.8).

Renal monitoring
Prior to initiating Emtricitabine/Tenofovir disoproxil Krka d.d. for the treatment of HIV-1 infection, it is recommended that creatinine clearance is calculated in all individuals.

In individuals without risk factors for renal disease, it is recommended that renal function (creatinine clearance and serum phosphate) is monitored after two to four weeks of use, after three months of use and every three to six months thereafter.

In individuals at risk for renal disease more frequent monitoring of renal function is required.

See also under *Co-administration of other medicinal products* below.

Renal management in HIV-1 infected patients
If serum phosphate is < 1.5 mg/dL (0.48 mmol/L) or creatinine clearance is decreased to < 50 mL/min in any patient receiving Emtricitabine/Tenofovir disoproxil Krka d.d., renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Consideration should be given to interrupting treatment with Emtricitabine/Tenofovir disoproxil Krka d.d. in patients with creatinine clearance decreased to < 50 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L). Interrupting treatment with Emtricitabine/Tenofovir disoproxil Krka d.d. should also be considered in case of progressive decline of renal function when no other cause has been identified.

Renal safety with emtricitabine/tenofovir disoproxil has only been studied to a very limited degree in HIV-1 infected patients with impaired renal function (creatinine clearance < 80 mL/min). Dose interval adjustments are recommended for HIV-1 infected patients with creatinine clearance 30-49 mL/min (see section 4.2). Limited clinical study data suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response. Furthermore, in a small clinical study, a subgroup of patients with creatinine clearance between 50 and 60 mL/min who received tenofovir disoproxil in combination with emtricitabine every 24 hours had a 2-4-fold higher exposure to tenofovir and worsening of renal function (see section 5.2). Therefore, a careful benefit-risk assessment is needed when Emtricitabine/Tenofovir disoproxil Krka d.d. is used in patients with creatinine clearance < 60 mL/min, and renal function should be closely monitored. In addition, the clinical response to treatment should be closely monitored in patients receiving Emtricitabine/Tenofovir disoproxil Krka d.d. at a prolonged dosing interval. The use of Emtricitabine/Tenofovir disoproxil Krka d.d. is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min) and in patients who require haemodialysis since appropriate dose reductions cannot be achieved with the combination tablet (see sections 4.2 and 5.2).

Bone effects

Bone abnormalities such as osteomalacia which can manifest as persistent or worsening bone pain, and which can infrequently contribute to fractures, may be associated with tenofovir disoproxil-induced proximal renal tubulopathy (see section 4.8).

If bone abnormalities are suspected or detected then appropriate consultation should be obtained.

Treatment of HIV-1 infection
Reductions of bone mineral density (BMD) have been observed with tenofovir disoproxil in randomized controlled clinical trials of duration up to 144 weeks in HIV or HBV-infected patients. These BMD decreases generally improved after treatment discontinuation.

In other studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor. Overall in view of the bone abnormalities associated with tenofovir disoproxil and the limitations of long term data on the impact of tenofovir disoproxil on bone health and fracture risk, alternative treatment regimens should be considered for patients with osteoporosis or with a history of bone fractures..

Renal and bone effects in the paediatric population

There are uncertainties associated with the long-term renal and bone effects of tenofovir disoproxilduring the treatment of HIV-1 infection in the paediatric population. Moreover, the reversibility of renal toxicity cannot be fully ascertained.

A multidisciplinary approach is recommended to weigh the benefit/risk balance of the use of emtricitabine/tenofovir, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation on a case by case basis.

Renal effects
Renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV 1 infected paediatric patients aged 2 to < 12 years in clinical study GS-US-104-0352 (see sections 4.8 and 5.1).

Renal monitoring
Renal function (creatinine clearance and serum phosphate) should be evaluated prior to treatment, and should be monitored during use as in adults (see above).

Renal management
If serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any paediatric patient receiving Emtricitabine/Tenofovir disoproxil Krka d.d., renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of emtricitabine/tenofovir disoproxil use. Interrupting use of Emtricitabine/Tenofovir disoproxil Krka d.d. should also be considered in case of progressive decline of renal function when no other cause has been identified.

Co-administration and risk of renal toxicity
The same recommendations apply as in adults (see Co-administration of other medicinal products below).

Renal impairment
The use of Emtricitabine/Tenofovir disoproxil Krka d.d. is not recommended in individuals under the age 18 years with renal impairment (see section 4.2). Emtricitabine/Tenofovir disoproxil Krka d.d. should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during Emtricitabine/Tenofovir disoproxil Krka d.d. use.

Bone effects
Use of tenofovir disoproxil may cause a reduction in BMD. The effects of tenofovir disoproxil - associated changes in BMD on long-term bone health and future fracture risk are currently unknown (see section 5.1).

If bone abnormalities are detected or suspected during use of emtricitabine/tenofovir disoproxil in any paediatric patient, consultation with an endocrinologist and/or nephrologist should be obtained.

Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

Mitochondrial dysfunction following exposure *in utero*

Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed *in utero* and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed *in utero* to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections

HIV-1 infected patients receiving Emtricitabine/Tenofovir disoproxil Krka d.d. or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV-disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Co-administration of other medicinal products

Use of Emtricitabine/Tenofovir disoproxil Krka d.d. should be avoided with concurrent or recent use of a nephrotoxic medicinal product (see section 4.5). If concomitant use with nephrotoxic agents is unavoidable, renal function should be monitored weekly.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in HIV-1 infected patients treated with tenofovir disoproxil and with risk factors for renal dysfunction. If Emtricitabine/Tenofovir disoproxil Krka d.d. is co-administered with an NSAID, renal function should be monitored adequately.

A higher risk of renal impairment has been reported in HIV-1 infected patients receiving tenofovir disoproxil in combination with a ritonavir or cobicistat boosted protease inhibitor. Close monitoring of renal function is required in these patients (see section 4.5). In HIV-1 infected patients with renal risk factors, the co-administration of tenofovir disoproxil with a boosted protease inhibitor should be carefully evaluated.

Emtricitabine/Tenofovir disoproxil Krka d.d. should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil, tenofovir alafenamide, or other cytidine analogues, such as lamivudine (see section 4.5). Emtricitabine/Tenofovir disoproxil Krka d.d. should not be administered concomitantly with adefovir dipivoxil.

Use with ledipasvir and sofosbuvir, sofosbuvir and velpatasvir or sofosbuvir, velpatasvir and voxilaprevir
Co-administration of tenofovir disoproxil with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir disoproxil and a pharmacokinetic enhancer (ritonavir or cobicistat).

The safety of tenofovir disoproxil when co-administered with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir concomitantly with tenofovir disoproxil and a boosted HIV protease inhibitor should be monitored for adverse reactions related to tenofovir disoproxil.

Co-administration of tenofovir disoproxil and didanosine:
Co-administration of tenofovir disoproxil and didanosine is not recommended (see section 4.5).

Triple nucleoside therapy

There have been reports of a high rate of virological failure and of emergence of resistance at an early stage in HIV-1 infected patients when tenofovir disoproxil was combined with lamivudine and abacavir as well as with lamivudine and didanosine as a once daily regimen. There is close structural similarity between lamivudine and emtricitabine and similarities in the pharmacokinetics and pharmacodynamics of these two agents. Therefore, the same problems may be seen if Emtricitabine/Tenofovir disoproxil Krka d.d. is administered with a third nucleoside analogue.

Elderly

Emtricitabine/tenofovir disoproxil has not been studied in individuals over the age of 65 years. Individuals over the age of 65 years are more likely to have decreased renal function, therefore caution should be exercised when administering Emtricitabine/Tenofovir disoproxil Krka d.d. to older people.

Lactose

Emtricitabine/Tenofovir disoproxil Krka d.d. contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

Emtricitabine/Tenofovir disoproxil Krka d.d. contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

As Emtricitabine/Tenofovir disoproxil Krka d.d. contains emtricitabine and tenofovir disoproxil, any interactions that have been identified with these agents individually may occur with Emtricitabine/Tenofovir disoproxil Krka d.d.. Interaction studies have only been performed in adults.

The steady-state pharmacokinetics of emtricitabine and tenofovir were unaffected when emtricitabine and tenofovir disoproxil were administered together *versus* each medicinal product dosed alone.

In vitro and clinical pharmacokinetic interaction studies have shown the potential for CYP450 mediated interactions involving emtricitabine and tenofovir disoproxil with other medicinal products is low.

Concomitant use not recommended

Emtricitabine/Tenofovir disoproxil Krka d.d. should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil, tenofovir alafenamide or other cytidine analogues, such as lamivudine (see section 4.4). Emtricitabine/Tenofovir disoproxil Krka d.d. should not be administered concomitantly with adefovir dipivoxil.

Didanosine: The co-administration of Emtricitabine/Tenofovir disoproxil Krka d.d. and didanosine is not recommended (see section 4.4 and Table 2).

Renally eliminated medicinal products: Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of Emtricitabine/Tenofovir disoproxil Krka d.d. with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicinal products.

Use of Emtricitabine/Tenofovir disoproxil Krka d.d. should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (see section 4.4).

Other interactions

Interactions between emtricitabine/tenofovir disoproxil or its individual component(s) and other medicinal products are listed in Table 2 below (increase is indicated as "↑", decrease as "↓", no change as "↔", twice daily as "b.i.d." and once daily as "q.d."). If available, 90% confidence intervals are shown in parentheses.

Table 2: Interactions between the individual components of emtricitabine/tenofovir disoproxil and other medicinal products

Medicinal product by therapeutic areas	**Effects on drug levels Mean percent change in AUC, C_{max}, C_{min} with 90% confidence intervals if available (mechanism)**	**Recommendation concerning co-administration with Emtricitabine/Tenofovir disoproxil Krka d.d. (emtricitabine 200 mg, tenofovir disoproxil 245 mg)**
ANTI-INFECTIVES		
Antiretrovirals		

Protease inhibitors		
Atazanavir/Ritonavir/Tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.)	Atazanavir: AUC: ↓ 25% (↓ 42 to ↓ 3) C_{max}: ↓ 28% (↓ 50 to ↑ 5) C_{min}: ↓ 26% (↓ 46 to ↑ 10) Tenofovir: AUC: ↑ 37% C_{max}: ↑ 34% C_{min}: ↑ 29%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Atazanavir/Ritonavir/Emtricitabine	Interaction not studied.	
Darunavir/Ritonavir/Tenofovir disoproxil (300 mg q.d./100 mg q.d./245 mg q.d.)	Darunavir: AUC: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 22% C_{min}: ↑ 37%	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Darunavir/Ritonavir/Emtricitabine	Interaction not studied.	
Lopinavir/Ritonavir/Tenofovir disoproxil (400 mg b.i.d./100 mg b.i.d/245 mg q.d.)	Lopinavir/Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 32% (↑ 25 to ↑ 38) C_{max}: ↔ C_{min}: ↑ 51% (↑ 37 to ↑ 66)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate tenofovir associated adverse events, including renal disorders. Renal function should be closely monitored (see section 4.4).
Lopinavir/Ritonavir/Emtricitabine	Interaction not studied.	
NRTIs		
Didanosine/Tenofovir disoproxil	Co-administration of tenofovir disoproxil and didanosine results in a 40-60% increase in systemic exposure to didanosine.	Co-administration of Emtricitabine/Tenofovir disoproxil Krka d.d. and didanosine is not recommended (see section 4.4). Increased systemic exposure to didanosine may increase didanosine related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.
Didanosine/Emtricitabine	Interaction not studied.	
Lamivudine/Tenofovir disoproxil	Lamivudine: AUC: ↓ 3% (↓ 8% to ↑ 15) C_{max}: ↓ 24% (↓ 44 to ↓ 12) C_{min}: NC Tenofovir:	Lamivudine and Emtricitabine/Tenofovir disoproxil Krka d.d. should not be administered concomitantly (see section 4.4).

	AUC: ↓ 4% (↓ 15 to ↑ 8) C_{max}: ↑ 102% (↓ 96 to ↑ 108) C_{min}: NC	
Efavirenz/Tenofovir disoproxil	Efavirenz: AUC: ↓ 4% (↓ 7 to ↓ 1) C_{max}: ↓ 4% (↓ 9 to ↑ 2) C_{min}: NC Tenofovir: AUC: ↓ 1% (↓ 8 to ↑ 6) C_{max}: ↑ 7% (↓ 6 to ↑ 22) C_{min}: NC	No dose adjustment of efavirenz is required.
ANTI-INFECTIVES		
Hepatitis B virus (HBV) antiviral agents		
Adefovir dipivoxil /Tenofovir disoproxil	Adefovir dipivoxil: AUC: ↓ 11% (↓ 14 to ↓ 7) C_{max}: ↓ 7% (↓ 13 to ↓ 0) C_{min}: NC Tenofovir: AUC: ↓ 2% (↓ 5 to ↑ 0) C_{max}: ↓ 1% (↓ 7 to ↑ 6) C_{min}: NC	Adefovir dipivoxil and Emtricitabine/Tenofovir disoproxil Krka d.d. should not be administered concomitantly (see section 4.4).
Hepatitis C virus (HCV) antiviral agents		
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)[1]	Ledipasvir: AUC: ↑ 96% (↑ 74 to ↑ 121) C_{max}: ↑ 68% (↑ 54 to ↑ 84) C_{min}: ↑ 118% (↑ 91 to ↑ 150) Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 42% (↑ 34 to ↑ 49) Atazanavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 63% (↑ 45 to ↑ 84) Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 45% (↑ 27 to ↑ 64) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 47% (↑ 37 to ↑ 58) C_{min}: ↑ 47% (↑ 38 to ↑ 57)	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)[1]	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↓ 27% (↓ 35 to ↓ 18) C_{max}: ↓ 37% (↓ 48 to ↓ 25) GS-331007[2]:	Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, ledipasvir/sofosbuvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when

	AUC: ↔ C_{max}: ↔ C_{min}: ↔ Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Ritonavir: AUC: ↔ C_{max}: ↔ C_{min}: ↑ 48% (↑ 34 to ↑ 63) Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 50% (↑ 42 to ↑ 59) C_{max}: ↑ 64% (↑ 54 to ↑ 74) C_{min}: ↑ 59% (↑ 49 to ↑ 70)	used with ledipasvir/sofosbuvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring, if other alternatives are not available (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Ledipasvir: AUC: ↓ 34% (↓ 41 to ↓ 25) C_{max}: ↓ 34% (↓ 41 to ↑ 25) C_{min}: ↓ 34% (↓ 43 to ↑ 24) Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 98% (↑ 77 to ↑ 123) C_{max}: ↑ 79% (↑ 56 to ↑ 104) C_{min}: ↑ 163% (↑ 137 to ↑ 197)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Emtricitabine/Rilpivirine/ Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.)	Ledipasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Sofosbuvir: AUC: ↔ C_{max}: ↔ GS-331007[2]: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Rilpivirine: AUC: ↔	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).

	C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 40% (↑ 31 to ↑ 50) C_{max}: ↔ C_{min}: ↑ 91% (↑ 74 to ↑ 110)	
Ledipasvir/Sofosbuvir (90 mg/400 mg q.d.) + Dolutegravir (50 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2] AUC: ↔ Cmax: ↔ Cmin: ↔ Ledipasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Dolutegravir AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 65% (↑ 59 to ↑ 71) Cmax: ↑ 61% (↑ 51 to ↑ 72) Cmin: ↑ 115% (↑ 105 to ↑ 126)	No dose adjustment is required. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Atazanavir/Ritonavir (300 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↑ 42% (↑ 37 to ↑ 49) Velpatasvir: AUC: ↑ 142% (↑ 123 to ↑ 164) Cmax: ↑ 55% (↑ 41 to ↑ 71) Cmin: ↑ 301% (↑ 257 to ↑ 350) Atazanavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 39% (↑ 20 to ↑ 61) Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↑ 29% (↑ 15 to ↑ 44) Emtricitabine:	Increased plasma concentrations of tenofovir resulting from co administration of tenofovir disoproxil, sofosbuvir/velpatasvir and atazanavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).

	AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↔ Cmax: ↑ 55% (↑ 43 to ↑ 68) Cmin: ↑ 39% (↑ 31 to ↑ 48)	
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Darunavir/Ritonavir (800 mg q.d./100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↓ 28% (↓ 34 to ↓ 20) Cmax: ↓ 38% (↓ 46 to ↓ 29) GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↓ 24% (↓ 35 to ↓ 11) Cmin: ↔ Darunavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 39% (↑ 33 to ↑ 44) Cmax: ↑ 55% (↑ 45 to ↑ 66) Cmin: ↑ 52% (↑ 45 to ↑ 59)	Increased plasma concentrations of tenofovir resulting from co administration of tenofovir disoproxil, sofosbuvir/velpatasvir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Lopinavir/Ritonavir (800 mg/200 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↓ 29% (↓ 36 to ↓ 22) Cmax: ↓ 41% (↓ 51 to ↓ 29) GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↓ 30% (↓ 41 to ↓ 17) Cmin: ↑ 63% (↑ 43 to ↑ 85) Lopinavir: AUC: ↔ Cmax: ↔ Cmin: ↔	Increased plasma concentrations of tenofovir resulting from co administration of tenofovir disoproxil, sofosbuvir/velpatasvir and lopinavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).

	Ritonavir: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↔ Cmax: ↑ 42% (↑ 27 to ↑ 57) Cmin: ↔	
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Raltegravir (400 mg b.i.d) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Raltegravir: AUC: ↔ Cmax: ↔ Cmin: ↓ 21% (↓ 58 to ↑ 48) Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 40% (↑ 34 to ↑ 45) Cmax: ↑ 46% (↑ 39 to ↑ 54) Cmin: ↑ 70% (↑ 61 to ↑ 79)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↑ 38% (↑ 14 to ↑ 67) GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↓ 53% (↓ 61 to ↓ 43) Cmax: ↓ 47% (↓ 57 to ↓ 36) Cmin: ↓ 57% (↓ 64 to ↓ 48) Efavirenz: AUC: ↔	Concomitant administration of sofosbuvir/velpatasvir and efavirenz is expected to decrease plasma concentrations of velpatasvir. Co administration of sofosbuvir/velpatasvir with efavirenz-containing regimens is not recommended.

	Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 81% (↑ 68 to ↑ 94) Cmax: ↑ 77% (↑ 53 to ↑ 104) Cmin: ↑ 121% (↑ 100 to ↑ 143)	
Sofosbuvir/Velpatasvir (400 mg/100 mg q.d.) + Emtricitabine/Rilpivirine/Tenofovir disoproxil (200 mg/25 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ Cmax: ↔ GS-331007[2]: AUC: ↔ Cmax: ↔ Cmin: ↔ Velpatasvir: AUC: ↔ Cmax: ↔ Cmin: ↔ Emtricitabine: AUC: ↔ Cmax: ↔ Cmin: ↔ Rilpivirine: AUC: ↔ Cmax: ↔ Cmin: ↔ Tenofovir: AUC: ↑ 40% (↑ 34 to ↑ 46) Cmax: ↑ 44% (↑ 33 to ↑ 55) Cmin: ↑ 84% (↑ 76 to ↑ 92)	No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4).

Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/ 100 mg+100 mg q.d.)[3] + Darunavir (800 mg q.d.) + Ritonavir (100 mg q.d.) + Emtricitabine/Tenofovir disoproxil (200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 30% C_{min}: N/A GS-331007[2]: AUC: ↔ C_{max}:↔ C_{min}: N/A Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Voxilaprevir: AUC: ↑ 143% C_{max}:↑ 72% C_{min}: ↑ 300% Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 34% Ritonavir: AUC: ↑ 45% C_{max}: ↑ 60% C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↑ 39% C_{max}: ↑ 48% C_{min}: ↑ 47%	Increased plasma concentrations of tenofovir resulting from co administration of tenofovir disoproxil, sofosbuvir/velpatasvir/voxilaprevir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).
Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 19% (↓ 40 to ↑ 10) GS-331007[2]: AUC: ↔ C_{max}: ↓ 23% (↓ 30 to ↑ 16) Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 25% (↑ 8 to ↑ 45) C_{min}: ↔	No dose adjustment is required.
Ribavirin/Tenofovir disoproxil	Ribavirin: AUC: ↑ 26% (↑ 20 to ↑ 32)	No dose adjustment of ribavirin is required.

	C_{max}: ↓ 5% (↓ 11 to ↑ 1) C_{min}: NC	
Herpes virus antiviral agents		
Famciclovir/Emtricitabine	Famciclovir: AUC: ↓ 9% (↓ 16 to ↓ 1) C_{max}: ↓ 7% (↓ 22 to ↑ 11) C_{min}: NC Emtricitabine: AUC: ↓ 7% (↓ 13 to ↓ 1) C_{max}: ↓ 11% (↓ 20 to ↑ 1) C_{min}: NC	No dose adjustment of famciclovir is required.
Antimycobacterials		
Rifampicin/Tenofovir disoproxil	Tenofovir: AUC: ↓ 12% (↓ 16 to ↓ 8) C_{max}: ↓ 16% (↓ 22 to ↓ 10) C_{min}: ↓ 15% (↓ 12 to ↓ 9)	No dose adjustment is required.
ORAL CONTRACEPTIVES		
Norgestimate/Ethinyl oestradiol/Tenofovir disoproxil	Norgestimate: AUC: ↓ 4% (↓ 32 to ↑ 34) C_{max}: ↓ 5% (↓ 27 to ↑ 24) C_{min}: NC Ethinyl oestradiol: AUC: ↓ 4% (↓ 9 to ↑ 0) C_{max}: ↓ 6% (↓ 13 to ↑ 0) C_{min}: ↓ 2% (↓ 9 to ↑ 6)	No dose adjustment of norgestimate/ethinyl oestradiol is required.
IMMUNOSUPPRESSANTS		
Tacrolimus/Tenofovir disoproxil /Emtricitabine	Tacrolimus: AUC: ↑ 4% (↓ 3 to ↑ 11) C_{max}: ↑ 3% (↓ 3 to ↑ 9) C_{min}: NC Emtricitabine: AUC: ↓ 5% (↓ 9 to ↓ 1) C_{max}: ↓ 11% (↓ 17 to ↓ 5) C_{min}: NC Tenofovir: AUC: ↑ 6% (↓ 1 to ↑ 13) C_{max}: ↑13% (↑ 1 to ↑ 27) C_{min}: NC	No dose adjustment of tacrolimus is required.
NARCOTIC ANALGESICS		
Methadone/Tenofovir disoproxil	Methadone: AUC: ↑ 5% (↓ 2 to ↑ 13) C_{max}: ↑ 5% (↓ 3 to ↑ 14) C_{min}: NC	No dose adjustment of methadone is required.

NC = not calculated.
N/A = not applicable.
[1] Data generated from simultaneous dosing with ledipasvir/sofosbuvir. Staggered administration (12 hours apart) provided similar results.
[2] The predominant circulating metabolite of sofosbuvir.
[3] Study conducted with additional voxilaprevir 100 mg to achieve voxilaprevir exposures expected in HCV-infected patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women (more than 1 000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil.

Animal studies on emtricitabine and tenofovir disoproxil do not indicate reproductive toxicity (see section 5.3). Therefore the use of Emtricitabine/Tenofovir disoproxil Krka d.d. may be considered during pregnancy, if necessary.

Breast-feeding

Emtricitabine and tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of emtricitabine and tenofovir in newborns/infants. Therefore Emtricitabine/Tenofovir disoproxil Krka d.d. should not be used during breast-feeding.

In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed their infants.

Fertility

No human data on the effect of emtricitabine/tenofovir disoproxil are available. Animal studies do not indicate harmful effects of emtricitabine or tenofovir disoproxil on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, individuals should be informed that dizziness has been reported during treatment with both emtricitabine and tenofovir disoproxil.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions considered possibly or probably related to emtricitabine and/or tenofovir disoproxil were nausea (12%) and diarrhoea (7%) in an open-label randomised clinical study in adults (GS-01-934, see section 5.1). The safety profile of emtricitabine and tenofovir disoproxil in this study was consistent with the previous experience with these agents when each was administered with other antiretroviral agents.

Tabulated summary of adverse reactions

The adverse reactions considered at least possibly related to treatment with the tenofovir disoproxil and emtricitabine from clinical study and post-marketing experience in HIV-1 infected patients are listed in Table 3, below, by body system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100) or rare (≥ 1/10 000 to < 1/1 000).

Table 3: Tabulated summary of adverse reactions associated with tenofovir disoproxil and emtricitabine based on clinical study and post-marketing experience

Frequency	**Emtricitabine**	**Tenofovir disoproxil**
Blood and lymphatic system disorders:		
Common:	neutropenia	
Uncommon:	anaemia[2]	
Immune system disorders:		
Common:	allergic reaction	
Metabolism and nutrition disorders:		
Very common:		hypophosphataemia[1]

Common:	hyperglycaemia, hypertriglyceridaemia	
Uncommon:		hypokalaemia[1]
Rare:		lactic acidosis
Psychiatric disorders:		
Common:	insomnia, abnormal dreams	
Nervous system disorders:		
Very common:	headache	dizziness
Common:	dizziness	headache
Gastrointestinal disorders:		
Very common:	diarrhoea, nausea	diarrhoea, vomiting, nausea
Common:	elevated amylase including elevated pancreatic amylase, elevated serum lipase, vomiting, abdominal pain, dyspepsia	abdominal pain, abdominal distension, flatulence
Uncommon:		pancreatitis
Hepatobiliary disorders:		
Common:	elevated serum aspartate aminotransferase (AST) and/or elevated serum alanine aminotransferase (ALT), hyperbilirubinaemia	increased transaminases
Rare:		hepatic steatosis, hepatitis
Skin and subcutaneous tissue disorders:		
Very common:		rash
Common:	vesiculobullous rash, pustular rash, maculopapular rash, rash, pruritus, urticaria, skin discolouration (increased pigmentation)[2]	
Uncommon:	angioedema[3]	
Rare:		angioedema
Musculoskeletal and connective tissue disorders:		
Very common:	elevated creatine kinase	
Common		bone mineral density decreased
Uncommon:		rhabdomyolysis[1], muscular weakness[1]
Rare:		osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1,3], myopathy[1]
Renal and urinary disorders:		
Uncommon:		increased creatinine, proteinuria, proximal renal tubulopathy including Fanconi syndrome
Rare:		renal failure (acute and chronic), acute tubular necrosis, nephritis (including acute interstitial nephritis)[3], nephrogenic diabetes insipidus
General disorders and administration site conditions:		
Very common:		asthenia

Common:	pain, asthenia	

[1] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil in the absence of this condition.
[2] Anaemia was common and skin discolouration (increased pigmentation) was very common when emtricitabine was administered to paediatric patients.
[3] This adverse reaction was identified through post-marketing surveillance but not observed in randomised controlled clinical studies in adults or paediatric HIV clinical studies for emtricitabine or in randomised controlled clinical studies or the tenofovir disoproxil expanded access program for tenofovir disoproxil. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in randomised controlled clinical studies (n = 1,563) or tenofovir disoproxil in randomised controlled clinical studies and the expanded access program (n = 7,319).

Description of selected adverse reactions

Renal impairment: As Emtricitabine/Tenofovir disoproxil Krka d.d. may cause renal damage monitoring of renal function is recommended (see section 4.4). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some HIV-1 infected patients, declines in creatinine clearance did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

Lactic acidosis: Cases of lactic acidosis have been reported with tenofovir disoproxil alone or in combination with other antiretrovirals. Patients with predisposing factors such as patients with decompensated liver disease, or patients receiving concomitant medications known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during tenofovir disoproxil treatment, including fatal outcomes.

Metabolic parameters: Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4).

Immune Reactivation Syndrome: In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Osteonecrosis: Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to CART. The frequency of this is unknown (see section 4.4).

Paediatric population

Assessment of adverse reactions related to emtricitabine is based on experience in three paediatric studies (n = 169) where treatment-naïve (n = 123) and treatment-experienced (n = 46) paediatric HIV infected patients aged 4 months to 18 years were treated with emtricitabine in combination with other antiretroviral agents. In addition to the adverse reactions reported in adults, anaemia (9.5%) and skin discolouration (31.8%) occurred more frequently in clinical trials in paediatric patients than in adults (see section 4.8, Tabulated summary of adverse reactions).

Assessment of adverse reactions related to tenofovir disoproxil is based on two randomised trials (studies GS-US-104-0321 and GS-US-104-0352) in 184 HIV 1 infected paediatric patients (aged 2 to < 18 years) who received treatment with tenofovir disoproxil (n = 93) or placebo/active comparator (n = 91) in combination with other antiretroviral agents for 48 weeks (see section 5.1). The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil were consistent with those observed in clinical studies of tenofovir disoproxil in adults (see section 4.8

Tabulated summary of adverse reactions and 5.1).

Reductions in BMD have been reported in paediatric patients. In HIV 1 infected adolescents (aged 12 to < 18 years), the BMD Z scores observed in subjects who received tenofovir disoproxil were lower than those observed in subjects who received placebo. In HIV 1 infected children (aged 2 to 15 years), the BMD Z scores observed in subjects who switched to tenofovir disoproxil were lower than those observed in subjects who remained on their stavudine- or zidovudine-containing regimen (see sections 4.4 and 5.1).

In study GS-US-104-0352, 89 HIV-1 infected paediatric patients with a median age of 7 years (range 2 to 15 years) were exposed to tenofovir disoproxil for a median of 331 weeks. Eight of the 89 patients (9.0%) discontinued study drug due to renal adverse events. Five subjects (5.6%) had laboratory findings clinically consistent with proximal renal tubulopathy, 4 of whom discontinued tenofovir disoproxil therapy. Seven patients had estimated glomerular filtration rate (GFR) values between 70 and 90 mL/min/1.73 m2. Among them, 3 patients experienced a clinically meaningful decline in estimated GFR during therapy which improved after discontinuation of tenofovir disoproxil.

Other special populations

Individuals with renal impairment: Since tenofovir disoproxil can cause renal toxicity, close monitoring of renal function is recommended in any adults with renal impairment receiving Emtricitabine/Tenofovir disoproxil Krka d.d. (see sections 4.2, 4.4 and 5.2). The use of Emtricitabine/Tenofovir disoproxil Krka d.d. is not recommended in individuals under the age of 18 years with renal impairment (see sections 4.2 and 4.4).

HIV/HBV or HCV co-infected patients: The adverse reaction profile of emtricitabine and tenofovir disoproxil in a limited number of HIV-infected patients in study GS-01-934 who were co-infected with HBV (n = 13) or HCV (n = 26) was similar to that observed in patients infected with HIV without co-infection. However, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

Exacerbations of hepatitis after discontinuation of treatment: In HBV infected patients, clinical and laboratory evidence of hepatitis have occurred after discontinuation of treatment (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

If overdose occurs the individual must be monitored for evidence of toxicity (see section 4.8), and standard supportive treatment applied as necessary.

Up to 30% of the emtricitabine dose and approximately 10% of the tenofovir dose can be removed by haemodialysis. It is not known whether emtricitabine or tenofovir can be removed by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use; antivirals for treatment of HIV infections, combinations. ATC code: J05AR03

Mechanism of action

Emtricitabine is a nucleoside analogue of cytidine. Tenofovir disoproxil is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Both emtricitabine and tenofovir have activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis B virus.

Emtricitabine and tenofovir are phosphorylated by cellular enzymes to form emtricitabine triphosphate and tenofovir diphosphate, respectively. *In vitro* studies have shown that both emtricitabine and tenofovir can be fully phosphorylated when combined together in cells. Emtricitabine triphosphate and tenofovir diphosphate competitively inhibit HIV-1 reverse transcriptase, resulting in DNA chain termination.

Both emtricitabine triphosphate and tenofovir diphosphate are weak inhibitors of mammalian DNA polymerases and there was no evidence of toxicity to mitochondria *in vitro* and *in vivo*.

Antiviral activity *in vitro*

Synergistic antiviral activity was observed with the combination of emtricitabine and tenofovir *in vitro*. Additive to synergistic effects were observed in combination studies with protease inhibitors, and with nucleoside and non-nucleoside analogue inhibitors of HIV reverse transcriptase.

Resistance

In vitro: Resistance has been seen *in vitro* and in some HIV-1 infected patients due to the development of the M184V/I mutation with emtricitabine or the K65R mutation with tenofovir. Emtricitabine-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir and zidovudine. The K65R mutation can also be selected by abacavir or didanosine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil should be avoided in patients with HIV-1 harbouring the K65R mutation. In addition, a K70E substitution in HIV-1 reverse transcriptase has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir. HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil.

In vivo - treatment of HIV-1: In an open-label randomised clinical study (GS-01-934) in antiretroviral-naïve patients, genotyping was performed on plasma HIV-1 isolates from all patients with confirmed HIV RNA > 400 copies/mL at weeks 48, 96 or 144 or at the time of early study drug discontinuation. As of week 144:

- The M184V/I mutation developed in 2/19 (10.5%) isolates analysed from patients in the emtricitabine/tenofovir disoproxil /efavirenz group and in 10/29 (34.5%) isolates analysed from the lamivudine/zidovudine/efavirenz group (p-value < 0.05, Fisher's Exact test comparing the emtricitabine+tenofovir disoproxil group to the lamivudine/zidovudine group among all patients).
- No virus analysed contained the K65R or K70E mutation.
- Genotypic resistance to efavirenz, predominantly the K103N mutation, developed in virus from 13/19 (68%) patients in the emtricitabine/tenofovir disoproxil /efavirenz group and in virus from 21/29 (72%) patients in the comparative group.

Clinical data

In an open-label randomised clinical study (GS-01-934), antiretroviral-naïve HIV-1 infected adult patients received either a once daily regimen of emtricitabine, tenofovir disoproxil and efavirenz (n = 255) or a fixed combination of lamivudine and zidovudineadministered twice daily and efavirenz once daily (n = 254). Patients in the emtricitabine and tenofovir disoproxil group were given emtricitabine/tenofovir disoproxil and efavirenz from week 96 to week 144. At baseline the randomised groups had similar median plasma HIV-1 RNA (5.02 and 5.00 $\log_{10}$ copies/mL) and CD4 counts (233 and 241 cells/mm^3). The primary efficacy endpoint for this study was the achievement and maintenance of confirmed HIV-1 RNA concentrations < 400 copies/mL over 48 weeks. Secondary efficacy analyses over 144 weeks included the proportion of patients with HIV-1 RNA concentrations < 400 or < 50 copies/mL, and change from baseline in CD4 cell count.

The 48-week primary endpoint data showed that the combination of emtricitabine, tenofovir disoproxil and efavirenz provided superior antiviral efficacy as compared with the fixed combination of lamivudine and zidovudine with efavirenz as shown in Table 4. The 144 week secondary endpoint data are also presented in Table 4.

Table 4: 48- and 144-week efficacy data from study GS-01-934 in which emtricitabine, tenofovir disoproxil and efavirenz were administered to antiretroviral-naïve patients with HIV-1 infection

	GS-01-934 Treatment for 48 weeks		**GS-01-934 Treatment for 144 weeks**	
	Emtricitabine+ tenofovir disoproxil +efavirenz	Lamivudine+ zidovudine+efavirenz	Emtricitabine+ tenofovir disoproxil +efavirenz*	Lamivudine+ zidovudine+efavirenz
HIV-1 RNA < 400 copies/mL (TLOVR)	84% (206/244)	73% (177/243)	71% (161/227)	58% (133/229)
p-value	0.002**		0.004**	
% difference (95%CI)	11% (4% to 19%)		13% (4% to 22%)	
HIV-1 RNA < 50 copies/mL (TLOVR)	80% (194/244)	70% (171/243)	64% (146/227)	56% (130/231)
p-value	0.021**		0.082**	
% difference (95%CI)	9% (2% to 17%)		8% (-1% to 17%)	
Mean change from baseline in CD4 cell count (cells/mm^3)	+190	+158	+312	+271
p-value	0.002[a]		0.089[a]	
Difference (95%CI)	32 (9 to 55)		41 (4 to 79)	

* Patients receiving emtricitabine, tenofovir disoproxil and efavirenz were given emtricitabine/tenofovir disoproxil plus efavirenz from week 96 to 144.
** The p-value based on the Cochran-Mantel-Haenszel Test stratified for baseline CD4 cell count
TLOVR = Time to Loss of Virologic Response
a: Van Elteren Test

In a randomised clinical study (M02-418), 190 antiretroviral-naïve adults were treated once daily with emtricitabine and tenofovir disoproxil in combination with lopinavir/ritonavir given once or twice daily. At 48 weeks, 70% and 64% of patients demonstrated HIV-1 RNA < 50 copies/mL with the once and twice daily regimens of lopinavir/ritonavir, respectively. The mean changes in CD4 cell count from baseline were +185 cells/mm^3 and +196 cells/mm^3, respectively.

Limited clinical experience in patients co-infected with HIV and HBV suggests that treatment with emtricitabine or tenofovir disoproxil in antiretroviral combination therapy to control HIV infection results in a reduction in HBV DNA (3 $\log_{10}$ reduction or 4 to 5 $\log_{10}$ reduction, respectively) (see

section 4.4).

Paediatric population

The safety and efficacy of emtricitabine/tenofovir disoproxil in children under the age of 12 years have not been established.

Treatment of HIV-1 infection in the paediatric population
There are no clinical studies conducted with emtricitabine/tenofovir disproxil in the paediatric population with HIV-1 infection.

Clinical efficacy and safety of emtricitabine/tenofovir disoproxil was established from studies conducted with emtricitabine and tenofovir disoproxil when given as single agents.

Studies with emtricitabine
In infants and children older than 4 months, the majority of patients taking emtricitabine achieved or maintained complete suppression of plasma HIV 1 RNA through 48 weeks (89% achieved ≤ 400 copies/mL and 77% achieved ≤ 50 copies/mL).

Studies with tenofovir disoproxil
In study GS-US-104-0321, 87 HIV 1 infected treatment-experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks. Due to limitations of the study, a benefit of tenofovir disoproxil over placebo was not demonstrated based on plasma HIV 1 RNA levels at week 24. However, a benefit is expected for the adolescent population based on extrapolation of adult data and comparative pharmacokinetic data (see section 5.2).

In patients who received treatment with tenofovir disoproxil or placebo, mean lumbar spine BMD Z score was -1.004 and -0.809, and mean total body BMD Z-score was -0.866 and -0.584, respectively, at baseline. Mean changes at week 48 (end of double-blind phase) were -0.215 and -0.165 in lumbar spine BMD Z-score, and -0.254 and -0.179 in total body BMD Z-score for the tenofovir disoproxil and placebo groups, respectively. The mean rate of BMD gain was less in the tenofovir disoproxil group compared to the placebo group. At week 48, six adolescents in the tenofovir disoproxil group and one adolescent in the placebo group had significant lumbar spine BMD loss (defined as > 4% loss). Among 28 patients receiving 96 weeks of treatment with tenofovir disoproxil, BMD Z scores declined by -0.341 for lumbar spine and -0.458 for total body.

In study GS-US-104-0352, 97 treatment-experienced patients 2 to < 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimens were randomised to either replace stavudine or zidovudine with tenofovir disoproxil (n = 48) or continue on their original regimen (n = 49) for 48 weeks. At week 48, 83% of patients in the tenofovir disoproxil treatment group and 92% of patients in the stavudine or zidovudine treatment group had HIV 1 RNA concentrations < 400 copies/mL. The difference in the proportion of patients who maintained < 400 copies/mL at week 48 was mainly influenced by the higher number of discontinuations in the tenofovir disoproxil treatment group. When missing data were excluded, 91% of patients in the tenofovir disoproxil treatment group and 94% of patients in the stavudine or zidovudine treatment group had HIV 1 RNA concentrations < 400 copies/mL at week 48.

Reductions in BMD have been reported in paediatric patients. In patients who received treatment with tenofovir disoproxil, or stavudine or zidovudine, mean lumbar spine BMD Z score was -1.034 and -0.498, and mean total body BMD Z-score was -0.471 and -0.386, respectively, at baseline. Mean changes at week 48 (end of randomised phase) were 0.032 and 0.087 in lumbar spine BMD Z score, and -0.184 and -0.027 in total body BMD Z score for the tenofovir disoproxil and stavudine or zidovudine groups, respectively. The mean rate of lumbar spine bone gain at week 48 was similar

between the tenofovir disoproxil treatment group and the stavudine or zidovudine treatment group. Total body bone gain was less in the tenofovir disoproxil treatment group compared to the stavudine or zidovudine treatment group. One tenofovir disoproxil treated subject and no stavudine or zidovudine treated subjects experienced significant (> 4%) lumbar spine BMD loss at week 48. BMD Z scores declined by -0.012 for lumbar spine and by -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil for 96 weeks. BMD Z scores were not adjusted for height and weight.

In study GS-US-104-0352, 8 out of 89 paediatric patients (9.0%) exposed to tenofovir disoproxil discontinued study drug due to renal adverse events. Five subjects (5.6%) had laboratory findings clinically consistent with proximal renal tubulopathy, 4 of whom discontinued tenofovir disoproxil therapy (median tenofovir disoproxil exposure 331 weeks).

5.2 Pharmacokinetic properties

Absorption

The bioequivalence of one emtricitabine/tenofovir disoproxil film-coated tablet with one emtricitabine 200 mg hard capsule and one tenofovir disoproxil 245 mg film-coated tablet was established following single dose administration to fasting healthy subjects. Following oral administration of emtricitabine/tenofovir disoproxil to healthy subjects, emtricitabine and tenofovir disoproxil are rapidly absorbed and tenofovir disoproxil is converted to tenofovir. Maximum emtricitabine and tenofovir concentrations are observed in serum within 0.5 to 3.0 h of dosing in the fasted state. Administration of emtricitabine/tenofovir disoproxil with food resulted in a delay of approximately three quarters of an hour in reaching maximum tenofovir concentrations and increases in tenofovir AUC and C_{max} of approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In order to optimise the absorption of tenofovir, it is recommended that Emtricitabine/Tenofovir disoproxil Krka d.d. should preferably be taken with food.

Distribution

Following intravenous administration the volume of distribution of emtricitabine and tenofovir was approximately 1.4 L/kg and 800 mL/kg, respectively. After oral administration of emtricitabine or tenofovir disoproxil, emtricitabine and tenofovir are widely distributed throughout the body. *In vitro* binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02 to 200 µg/mL. *In vitro* protein binding of tenofovir to plasma or serum protein was less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 µg/mL.

Biotransformation

There is limited metabolism of emtricitabine. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulphoxide diastereomers (approximately 9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (approximately 4% of dose). *In vitro* studies have determined that neither tenofovir disoproxil nor tenofovir are substrates for the CYP450 enzymes. Neither emtricitabine nor tenofovir inhibited *in vitro* drug metabolism mediated by any of the major human CYP450 isoforms involved in drug biotransformation. Also, emtricitabine did not inhibit uridine-5'-diphosphoglucuronyl transferase, the enzyme responsible for glucuronidation.

Elimination

Emtricitabine is primarily excreted by the kidneys with complete recovery of the dose achieved in urine (approximately 86%) and faeces (approximately 14%). Thirteen percent of the emtricitabine dose was recovered in urine as three metabolites. The systemic clearance of emtricitabine averaged 307 mL/min. Following oral administration, the elimination half-life of emtricitabine is approximately

10 hours.

Tenofovir is primarily excreted by the kidney by both filtration and an active tubular transport system with approximately 70-80% of the dose excreted unchanged in urine following intravenous administration. The apparent clearance of tenofovir averaged approximately 307 mL/min. Renal clearance has been estimated to be approximately 210 mL/min, which is in excess of the glomerular filtration rate. This indicates that active tubular secretion is an important part of the elimination of tenofovir. Following oral administration, the elimination half-life of tenofovir is approximately 12 to 18 hours.

Elderly

Pharmacokinetic studies have not been performed with emtricitabine or tenofovir (administered as tenofovir disoproxil) in the elderly (over 65 years of age).

Gender

Emtricitabine and tenofovir pharmacokinetics are similar in male and female patients.

Ethnicity

No clinically important pharmacokinetic difference due to ethnicity has been identified for emtricitabine. The pharmacokinetics of tenofovir (administered as tenofovir disoproxil) have not been specifically studied in different ethnic groups.

Paediatric population

Pharmacokinetic studies have not been performed with emtricitabine/tenofovir disoproxil in children and adolescents (under 18 years of age). Steady-state pharmacokinetics of tenofovir were evaluated in 8 HIV-1 infected adolescent patients (aged 12 to < 18 years) with body weight ≥ 35 kg and in 23 HIV-1 infected children aged 2 to < 12 years. Tenofovir exposure achieved in these paediatric patients receiving oral daily doses of tenofovir disoproxil 245 mg or 6.5 mg/kg body weight tenofovir disoproxil up to a maximum dose of 245 mg was similar to exposures achieved in adults receiving once-daily doses of tenofovir disoproxil 245 mg. Pharmacokinetic studies have not been performed with tenofovir disoproxil in children under 2 years. In general, the pharmacokinetics of emtricitabine in infants, children and adolescents (aged 4 months up to 18 years) are similar to those seen in adults.

Renal impairment

Limited pharmacokinetic data are available for emtricitabine and tenofovir after co-administration of separate preparations or as emtricitabine/tenofovir disoproxil in patients with renal impairment. Pharmacokinetic parameters were mainly determined following administration of single doses of emtricitabine 200 mg or tenofovir disoproxil 245 mg to non-HIV infected subjects with varying degrees of renal impairment. The degree of renal impairment was defined according to baseline creatinine clearance (CrCl) (normal renal function when CrCl > 80 mL/min; mild impairment with CrCl = 50-79 mL/min; moderate impairment with CrCl = 30-49 mL/min and severe impairment with CrCl = 10-29 mL/min).

The mean (%CV) emtricitabine drug exposure increased from 12 (25%) µg•h/mL in subjects with normal renal function, to 20 (6%) µg•h/mL, 25 (23%) µg•h/mL and 34 (6%) µg•h/mL, in subjects with mild, moderate and severe renal impairment, respectively. The mean (%CV) tenofovir drug exposure increased from 2,185 (12%) ng•h/mL in subjects with normal renal function, to 3,064 (30%) ng•h/mL, 6,009 (42%) ng•h/mL and 15,985 (45%) ng•h/mL, in subjects with mild, moderate and severe renal impairment, respectively.

The increased dose interval for emtricitabine/tenofovir disoproxil in HIV-1 infected patients with moderate renal impairment is expected to result in higher peak plasma concentrations and lower C_{min} levels as compared to patients with normal renal function. In subjects with end-stage renal disease (ESRD) requiring haemodialysis, between dialysis drug exposures substantially increased over 72 hours to 53 (19%) µg•h/mL of emtricitabine, and over 48 hours to 42,857 (29%) ng•h/mL of tenofovir.

A small clinical study was conducted to evaluate the safety, antiviral activity and pharmacokinetics of tenofovir disoproxil in combination with emtricitabine in HIV infected patients with renal impairment. A subgroup of patients with baseline creatinine clearance between 50 and 60 mL/min, receiving once daily dosing, had a 2-4-fold increase in tenofovir exposure and worsening renal function.

The pharmacokinetics of emtricitabine and tenofovir (administered as tenofovir disoproxil) in paediatric patients with renal impairment have not been studied. No data are available to make dose recommendations (see sections 4.2 and 4.4).

Hepatic impairment

The pharmacokinetics of emtricitabine/tenofovir disoproxil have not been studied in subjects with hepatic impairment.

The pharmacokinetics of emtricitabine have not been studied in non-HBV infected subjects with varying degrees of hepatic insufficiency. In general, emtricitabine pharmacokinetics in HBV infected subjects were similar to those in healthy subjects and in HIV infected patients.

A single 245 mg dose of tenofovir disoproxil was administered to non-HIV infected subjects with varying degrees of hepatic impairment defined according to Child-Pugh-Turcotte (CPT) classification. Tenofovir pharmacokinetics were not substantially altered in subjects with hepatic impairment suggesting that no dose adjustment is required in these subjects. The mean (%CV) tenofovir C_{max} and $AUC_{0-\infty}$ values were 223 (34.8%) ng/mL and 2,050 (50.8%) ng•h/mL, respectively, in normal subjects compared with 289 (46.0%) ng/mL and 2,310 (43.5%) ng•h/mL in subjects with moderate hepatic impairment, and 305 (24.8%) ng/mL and 2,740 (44.0%) ng•h/mL in subjects with severe hepatic impairment.

5.3 Preclinical safety data

Emtricitabine: Non-clinical data on emtricitabine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

Tenofovir disoproxil: Non-clinical safety pharmacology studies on tenofovir disoproxil reveal no special hazard for humans. Repeated dose toxicity studies in rats, dogs and monkeys at exposure levels greater than or equal to clinical exposure levels and with possible relevance to clinical use include renal and bone toxicity and a decrease in serum phosphate concentration. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced BMD (rats and dogs). The bone toxicity in young adult rats and dogs occurred at exposures ≥ 5-fold the exposure in paediatric or adult patients; bone toxicity occurred in juvenile infected monkeys at very high exposures following subcutaneous dosing (≥ 40-fold the exposure in patients). Findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in BMD.

Genotoxicity studies revealed positive results in the *in vitro* mouse lymphoma assay, equivocal results in one of the strains used in the Ames test, and weakly positive results in an UDS test in primary rat hepatocytes. However, it was negative in an *in vivo* mouse bone marrow micronucleus assay.

Oral carcinogenicity studies in rats and mice only revealed a low incidence of duodenal tumours at an extremely high dose in mice. These tumours are unlikely to be of relevance to humans.

Reproductive toxicity studies in rats and rabbits showed no effects on mating, fertility, pregnancy or foetal parameters. However, tenofovir disoproxil reduced the viability index and weight of pups in a periand postnatal toxicity study at maternally toxic doses.

Combination of emtricitabine and tenofovir disoproxil: Genotoxicity and repeated dose toxicity studies of one month or less with the combination of these two components found no exacerbation of toxicological effects compared to studies with the separate components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Pregelatinized starch
Croscarmellose sodium
Lactose monohydrate
Microcrystalline cellulose
Sodium stearyl fumarate
Stearic acid

Film coating
Hypromellose 5 cP
Titanium dioxide (E171)
Macrogol
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Shelf life after first opening of the bottle: 2 months.

6.4 Special precautions for storage

Blisters
Do not store above 30°C.
Store in the original blister in order to protect from moisture and light.

HDPE bottle
Do not store above 30°C.
Keep the bottle tightly closed in order to protect from moisture and light.

6.5 Nature and contents of container

Blisters

OPA/Alu/PE+DES/ - Aluminium blisters.
Pack sizes: 28 x 1 and 84 film-coated tablets.

HDPE bottle
High density polyethylene (HDPE) bottle with a child-resistant tamper evident polypropylene closure with integrated a silica gel desiccant.
Pack sizes: 30 film-coated tablets (1x30) and 90 film-coated tablets (3x30).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

Blisters
28 x 1 film-coated tablet: EU/1/17/1182/001
84 film-coated tablets: EU/1/17/1182/003

Bottle
30 film-coated tablets: EU/1/17/1182/002
90 (3 x 30) film-coated tablets: EU/1/17/1182/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 April 2017
Date of latest renewal: 6 January 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

TAD Pharma GmbH
Heinz-Lohmann-Straße 5
27472 Cuxhaven
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON/for blisters and bottle

1. NAME OF THE MEDICINAL PRODUCT

Emtricitabine/Tenofovir disoproxil Krka d.d. 200 mg/245 mg film-coated tablets

emtricitabine/tenofovir disoproxil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300.7 mg of tenofovir disoproxil succinate or 136 mg of tenofovir).

3. LIST OF EXCIPIENTS

Contains also lactose monohydrate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

for blisters:
28 x 1 film-coated tablet
84 film-coated tablets

for bottle:
30 film-coated tablets
90 (3 bottles of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
for bottle
Shelf life after first opening of the bottle: 2 months.
Date of opening:_____

9. SPECIAL STORAGE CONDITIONS

for blisters:
Do not store above 30°C.
Store in the original blister in order to protect from moisture and light.

for bottle:
Do not store above 30°C.
Keep the bottle tightly closed in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

for blister:
28 x 1 film-coated tablet: EU/1/17/1182/001
84 film-coated tablets: EU/1/17/1182/003

for bottle:
30 film-coated tablets: EU/1/17/1182/002
90 (3 x 30) film-coated tablets: EU/1/17/1182/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Emtricitabine/Tenofovir disoproxil Krka d.d.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (OPA/Alu/PE+DES–Alu FOIL) – for non unit dose blister

1. NAME OF THE MEDICINAL PRODUCT

Emtricitabine/Tenofovir disoproxil Krka d.d. 200 mg/245 mg film-coated tablets

emtricitabine/tenofovir disoproxil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (OPA/Alu/PE+DES–Alu FOIL) – for unit dose blister

1. NAME OF THE MEDICINAL PRODUCT

Emtricitabine/Tenofovir disoproxil Krka d.d. 200 mg/245 mg tablets

emtricitabine/tenofovir disoproxil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Emtricitabine/Tenofovir disoproxil Krka d.d. 200 mg/245 mg film-coated tablets

emtricitabine/tenofovir disoproxil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300.7 mg of tenofovir disoproxil succinate or 136 mg of tenofovir).

3. LIST OF EXCIPIENTS

Contains also lactose monohydrate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Shelf life after first opening of the bottle: 2 months.
Date of opening: _____

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Keep the bottle tightly closed in order to protect from moisture and light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Emtricitabine/Tenofovir disoproxil Krka d.d. 200 mg/245 mg film-coated tablets
emtricitabine/tenofovir disoproxil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Emtricitabine/Tenofovir disoproxil Krka d.d. is and what it is used for

Emtricitabine/Tenofovir disoproxil Krka d.d. contains two active substances, *emtricitabine* and *tenofovir disoproxil*. Both of these active substances are *antiretroviral* medicines which are used to treat HIV infection. Emtricitabine is a *nucleoside reverse transcriptase inhibitor* and tenofovir is a *nucleotide reverse transcriptase inhibitor.* However, both are generally known as NRTIs and they work by interfering with the normal working of an enzyme (reverse transcriptase) that is essential for the virus to reproduce itself.

- **Emtricitabine/Tenofovir disoproxil Krka d.d. is used to treat Human Immunodeficiency Virus 1 (HIV-1) infection in adults**.
- **It is also used to treat HIV in adolescents aged 12 to less than 18 years who weigh at least 35 kg**, and who have already been treated with other HIV medicines that are no longer effective or have caused side effects.

    - Emtricitabine/Tenofovir disoproxil Krka d.d. should always be used combined with other medicines to treat HIV infection.
    - Emtricitabine/Tenofovir disoproxil Krka d.d. can be administered in place of emtricitabine and tenofovir disoproxil used separately at the same doses.

This medicine is not a cure for HIV infection. While taking Emtricitabine/Tenofovir disoproxil Krka d.d. you may still develop infections or other illnesses associated with HIV infection.

2. What you need to know before you take Emtricitabine/Tenofovir disoproxil Krka d.d.

Do not take Emtricitabine/Tenofovir disoproxil Krka d.d.if you are allergic to emtricitabine, tenofovir, tenofovir disoproxil, or any of the other ingredients of this medicine (listed in section 6).

→ If this applies to you, tell your doctor immediately.

Warnings and precautions

While taking Emtricitabine/Tenofovir disoproxil Krka d.d. to treat HIV

- **Emtricitabine/Tenofovir disoproxil Krka d.d. may affect your kidneys.** Before and during treatment, your doctor may order blood tests to measure kidney function. Tell your doctor if you have had kidney disease, or if tests have shown kidney problems. Emtricitabine/Tenofovir disoproxil Krka d.d. should not be given to adolescents with existing kidney problems. If you have kidney problems, your doctor may advise you to stop taking Emtricitabine/Tenofovir disoproxil Krka d.d. or, if you already have HIV, to take Emtricitabine/Tenofovir disoproxil Krka d.d. less frequently. Emtricitabine/Tenofovir disoproxil Krka d.d. is not recommended if you have severe kidney disease or are on dialysis.

- **Talk to your doctor if you suffer from osteoporosis, have a history of bone fracture or if you have problems with your bones.**

  Bone problems (manifesting as persistent or worsening bone pain and sometimes resulting in fractures) may also occur due to damage to kidney tubule cells (see section 4, *Possible side effects*). Tell your doctor if you have bone pain or fractures.

  Tenofovir disoproxil may also cause loss of bone mass. The most pronounced bone loss was seen in clinical studies when patients were treated for HIV with tenofovir disoproxil in combination with a boosted protease inhibitor.

  Overall, the effects of tenofovir disoproxil on long term bone health and future fracture risk in adult and paediatric patients are uncertain.

- **Talk to your doctor if you have a history of liver disease, including hepatitis.** Patients infected with HIV who also have liver disease (including chronic hepatitis B or C), who are treated with antiretrovirals, have a higher risk of severe and potentially fatal liver complications. If you have hepatitis B or C, your doctor will carefully consider the best treatment regimen for you.

- **Know your hepatitis B virus (HBV) infection status** before starting Emtricitabine/Tenofovir disoproxil Krka d.d.. If you have HBV, there is a serious risk of liver problems when you stop taking Emtricitabine/Tenofovir disoproxil Krka d.d., whether or not you also have HIV. It is important not to stop taking Emtricitabine/Tenofovir disoproxil Krka d.d. without talking to your doctor: see section 3, *Do not stop taking Emtricitabine/Tenofovir disoproxil Krka d.d.*.

- **Talk to your doctor if you are over 65.** Emtricitabine/Tenofovir disoproxil Krka d.d. has not been studied in patients over 65 years of age.

- **Talk to your doctor if you are intolerant to lactose** (see Emtricitabine/Tenofovir disoproxil Krka d.d. contains lactose later in this section).

Children and adolescents

Emtricitabine/Tenofovir disoproxil Krka d.d. is not for use in children under 12 years of age.

Other medicines and Emtricitabine/Tenofovir disoproxil Krka d.d.

Do not take Emtricitabine/Tenofovir disoproxil Krka d.d. if you are already taking other medicines that contain the components of Emtricitabine/Tenofovir disoproxil Krka d.d. (emtricitabine and

tenofovir disoproxil) or any other antiviral medicines that contain tenofovir alafenamide, lamivudine or adefovir dipivoxil.

Taking Emtricitabine/Tenofovir disoproxil Krka d.d. with other medicines that can damage your kidneys: it is especially important to tell your doctor if you are taking any of these medicines, including
- aminoglycosides (for bacterial infection)
- amphotericin B (for fungal infection)
- foscarnet (for viral infection)
- ganciclovir (for viral infection)
- pentamidine (for infections)
- vancomycin (for bacterial infection)
- interleukin-2 (to treat cancer)
- cidofovir (for viral infection)
- non-steroidal anti-inflammatory drugs (NSAIDs, to relieve bone or muscle pains)

If you are taking another antiviral medicine called a protease inhibitor to treat HIV, your doctor may order blood tests to closely monitor your kidney function.

It is also important to tell your doctor if you are taking ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir to treat hepatitis C infection.

Taking Emtricitabine/Tenofovir disoproxil Krka d.d. with other medicines containing didanosine (for treatment of HIV infection): Taking Emtricitabine/Tenofovir disoproxil Krka d.d. with other antiviral medicines that contain didanosine can raise the levels of didanosine in your blood and may reduce CD4 cell counts. Rarely, inflammation of the pancreas and lactic acidosis (excess lactic acid in the blood), which sometimes causes death, have been reported when medicines containing tenofovir disoproxil and didanosine were taken together. Your doctor will carefully consider whether to treat you with combinations of tenofovir and didanosine.

→ **Tell your doctor** if you are taking any of these medicines. Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Emtricitabine/Tenofovir disoproxil Krka d.d. with food and drink

- Whenever possible, Emtricitabine/Tenofovir disoproxil Krka d.d. should be taken with food**.**

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you have taken Emtricitabine/Tenofovir disoproxil Krka d.d. during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.

- **Do not breast-feed during treatment with Emtricitabine/Tenofovir disoproxil Krka d.d..** This is because the active substances in this medicine pass into human breast milk.

- Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby in breast milk.

- If you are breast-feeding, or thinking about breast-feeding, you should **discuss it with your**

doctor as soon as possible.

Driving and using machines

Emtricitabine/Tenofovir disoproxil Krka d.d. can cause dizziness. If you feel dizzy while taking Emtricitabine/Tenofovir disoproxil Krka d.d., **do not drive** and do not use any tools or machines.

Emtricitabine/Tenofovir disoproxil Krka d.d. contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Emtricitabine/Tenofovir disoproxil Krka d.d. contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

3. How to take Emtricitabine/Tenofovir disoproxil Krka d.d.

- **Always take this medicine exactly as your doctor has told you.** Check with your doctor or pharmacist if you are not sure.

The recommended dose of Emtricitabine/Tenofovir disoproxil Krka d.d. is:

- **Adults:** one tablet each day, where possible, with food**.**

- **Adolescents aged 12 to less than 18 years who weigh at least 35 kg:** one tablet each day, whenever possible with food.

If you have difficulty swallowing, you can use the tip of a spoon to crush the tablet. Then mix the powder with about 100 mL (half a glass) of water, orange juice or grape juice, and drink immediately.

- **Always take the dose recommended by your doctor.** This is to make sure that your medicine is fully effective, and to reduce the risk of developing resistance to the treatment. Do not change the dose unless your doctor tells you to.

- Your doctor will prescribe Emtricitabine/Tenofovir disoproxil Krka d.d. with other antiretroviral medicines. Please refer to the patient information leaflets of the other antiretrovirals for guidance on how to take those medicines.

Ask your doctor if you have any questions about how to prevent getting HIV or prevent spreading HIV to other people.

If you take more Emtricitabine/Tenofovir disoproxil Krka d.d. than you should

If you accidentally take more than the recommended dose of Emtricitabine/Tenofovir disoproxil Krka d.d., contact your doctor or nearest emergency department for advice. Keep the tablet bottle with you so that you can easily describe what you have taken.

If you forget to take Emtricitabine/Tenofovir disoproxil Krka d.d.

It is important not to miss a dose of Emtricitabine/Tenofovir disoproxil Krka d.d..

- **If you notice within 12 hours** of the time you usually take Emtricitabine/Tenofovir disoproxil Krka d.d., take the tablet preferably with food as soon as possible. Then take the next dose at

your usual time.
- **If you notice 12 hours or more after** the time you usually take Emtricitabine/Tenofovir disoproxil Krka d.d., forget about the missed dose. Wait and take the next dose, preferably with food, at your usual time.

If you vomit less than 1 hour after taking Emtricitabine/Tenofovir disoproxil Krka d.d., take another tablet. You do not need to take another tablet if you were sick more than 1 hour after taking Emtricitabine/Tenofovir disoproxil Krka d.d..

If you stop taking Emtricitabine/Tenofovir disoproxil Krka d.d.

- Stopping tablets may reduce the effectiveness of the anti-HIV therapy recommended by your doctor.

→ Do not stop taking Emtricitabine/Tenofovir disoproxil Krka d.d. without contacting your doctor.

If you have hepatitis B, it is especially important not to stop your Emtricitabine/Tenofovir disoproxil Krka d.d. treatment without talking to your doctor first. You may require blood tests for several months after stopping treatment. In some patients with advanced liver disease or cirrhosis, stopping treatment is not recommended as this may lead to worsening of your hepatitis, which may be life-threatening.

→ **Tell your doctor immediately** about new or unusual symptoms after you stop treatment, particularly symptoms you associate with hepatitis B infection

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Possible serious side effects:

- **Lactic acidosis** (excess lactic acid in the blood) is a rare but potentially life-threatening side effect. Lactic acidosis occurs more often in women, particularly if they are overweight, and in people with liver disease. The following may be signs of lactic acidosis:
  - deep rapid breathing
  - drowsiness
  - feeling sick (nausea), being sick (vomiting)
  - stomach pain

  → If you think you may have lactic acidosis, get medical help immediately.

- **Any signs of inflammation or infection.** In some patients with advanced HIV infection (AIDS) and a history of opportunistic infections (infections that occur in people with a weak immune system), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started. It is thought that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

- **Autoimmune disorders**, when the immune system attacks healthy body tissue, may also occur after you start taking medicines to treat HIV infection. Autoimmune disorders may occur many months after the start of treatment. Look out for any symptoms of infection or other symptoms

such as:
- muscle weakness
- weakness beginning in the hands and feet and moving up towards the trunk of the body
- palpitations, tremor or hyperactivity

→ If you notice these or any symptoms of inflammation or infection, get medical help immediately.

Possible side effects:

Very common side effects
(may affect more than 1 in 10 people)
- diarrhoea, being sick (vomiting), feeling sick (nausea)
- dizziness, headache
- rash
- feeling weak

Tests may also show:
- decreases in phosphate in the blood
- increased creatine kinase

Common side effects
(may affect up to 1 in 10 people)
- pain, stomach pain
- difficulty sleeping, abnormal dreams
- problems with digestion resulting in discomfort after meals, feeling bloated, flatulence
- rashes (including red spots or blotches sometimes with blistering and swelling of the skin), which may be allergic reactions, itching, changes in skin colour including darkening of the skin in patches
- other allergic reactions, such as wheezing, swelling or feeling light-headed
- loss of bone mass

Tests may also show:
- low white blood cell count (a reduced white blood cell count can make you more prone to infection)
- increased triglycerides (fatty acids), bile or sugar in the blood
- liver and pancreas problems

Uncommon side effects
(may affect up to 1 in 100 people)
- pain in the abdomen (tummy) caused by inflammation of the pancreas
- swelling of the face, lips, tongue or throat
- anaemia (low red blood cell count)
- breakdown of muscle, muscle pain or weakness which may occur due to damage to the kidney tubule cells

Tests may also show:
- decreases in potassium in the blood
- increased creatinine in your blood
- changes to your urine

Rare side effects
(may affect up to 1 in 1 000 people)
- Lactic acidosis (see Possible serious side effects)
- fatty liver

- yellow skin or eyes, itching, or pain in the abdomen (tummy) caused by inflammation of the liver
- inflammation of the kidney, passing a lot of urine and feeling thirsty, kidney failure, damage to kidney tubule cells
- softening of the bones (with bone pain and sometimes resulting in fractures)
- back pain caused by kidney problems

Damage to kidney tubule cells may be associated with breakdown of muscle, softening of the bones (with bone pain and sometimes resulting in fractures), muscle pain, muscle weakness and decreases in potassium or phosphate in the blood.

→ **If you notice any of the side effects listed above or if any of the side effects get serious**, talk to your doctor or pharmacist.

The frequency of the following side effects is not known.
- **Bone problems.** Some patients taking combination antiretroviral medicines such as emtricitabine/tenofovir disoproxil may develop a bone disease called osteonecrosis (death of bone tissue caused by loss of blood supply to the bone). Taking this type of medicine for a long time, taking corticosteroids, drinking alcohol, having a very weak immune system, and being overweight, may be some of the many risk factors for developing this disease. Signs of osteonecrosis are:
  - joint stiffness
  - joint aches and pains (especially of the hip, knee and shoulder)
  - difficulty with movement

→ **If you notice any of these symptoms tell your doctor.**

During treatment for HIV there may be an increase in weight and in levels of blood lipids and glucose. This is partly linked to restored health and life style, and in the case of blood lipids sometimes to the HIV medicines themselves. Your doctor will test for these changes.

Other effects in children
- Children given emtricitabine very commonly experienced changes in skin colour including
  - darkening of the skin in patches
- Children commonly experienced low red blood cell count (anaemia).
  - This may cause the child to be tired or breathless

→ **If you notice any of these symptoms tell your doctor.**

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Emtricitabine/Tenofovir disoproxil Krka d.d.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

Blisters
Do not store above 30°C.
Store in the original blister in order to protect from moisture and light.

Bottle
Do not store above 30°C.
Keep the bottle tightly closed in order to protect from moisture and light.

Shelf life after first opening of the bottle: 2 months.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Emtricitabine/Tenofovir disoproxil Krka d.d. contains
- The active substances are emtricitabine and tenofovir disoproxil.
  Each tablet contains 200 mg of emtricitabine and 245 mg of tenofovir disoproxil (equivalent to 300.7 mg of tenofovir disoproxil succinate or 136 mg of tenofovir).
- The other ingredients are:
  Tablet core: pregelatinized starch, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, sodium stearyl fumarate, stearic acid.
  Film coating: hypromellose 5 cP, titanium dioxide (E171), macrogol, indigo carmine aluminium lake (E132). See section 2 "Emtricitabine/Tenofovir disoproxil Krka d.d. contains lactose", "Emtricitabine/Tenofovir disoproxil Krka d.d. contains sodium".

What Emtricitabine/Tenofovir disoproxil Krka d.d. looks like and contents of the pack
Emtricitabine/Tenofovir disoproxil Krka d.d. film-coated tablets (tablets) are blue, oval, biconvex tablets, of dimensions 20 mm x 10 mm.

Emtricitabine/Tenofovir disoproxil Krka d.d. is available in carton boxes of 28 x 1 and 84 film-coated tablets in blisters.

Emtricitabine/Tenofovir disoproxil Krka d.d. is available also in bottles of 30 tablets, with a child-resistant tamper evident plastic closure with integrated a silica gel desiccant, which helps to protect your tablets. The following pack sizes are available: outer cartons containing 1 bottle of 30 film-coated tablets and 90 (3 bottles of 30) film-coated tablets.
Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.